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Personalized Medicine: Genome-Wide Association Studies (GWAS)

According to a recent article titled "The Genome Gets Personal—Almost" published in the *Journal of the American Medical Association*, significant recent advances relevant to personalized medicine come from the current explosion of genome-wide association studies. These studies are based on the ability to search the genomes of large numbers of individuals in an unbiased way for statistical associations between the most common form of genetic variation, single nucleotide polymorphisms (SNPs), and the occurrence of disease. In the past year, genome-wide association studies yielded robust information on new genetic markers for common chronic diseases, including diabetes, heart disease, Crohn's disease, and several common cancers. REF #1

With genomics discoveries relating to common chronic diseases, numerous genetic tests that hold promise for significant changes in the delivery of health care, particularly in preventive medicine and in tailoring drug treatment, may emerge. The *Journal of the American Medical Association* has also recently published a systematic review of public articles, which were analyzed to synthesize current information on genetic health services for common adult-onset conditions. The authors examined studies that addressed the outcomes, consumer information needs, delivery, and challenges in integrating these services. REF #2

In 2007, the largest known GWAS was published by the Wellcome Trust Case Control Consortium—a collection of some 50 groups that pooled resources to study seven diseases across 14,000 people and a shared group of 3000 controls. Experts say that the excitement surrounding these projects is well deserved. This research was profiled in a May 2008 article in *Genome Technology*. REF #3

Nutrigenomics: Changing Clinical Nutrition and Public Health Practice

The maintenance of health and the prevention and treatment of chronic diseases are influenced by naturally occurring chemicals in food. In addition to supplying the substrates for producing energy, a large number of dietary chemicals are bioactive (that is, they alter the regulation of biological processes and, either directly or indirectly, the expression of genetic information. The study of nutrient-gene interactions has been christened nutrigenomics, a name and concept modeled on pharmacogenomics, which is the study of the genetic basis of an individual's response to drugs. The complexity of the genetic, nutrient intake, and physiological data can overwhelm standard statistical analyses method; however, explorations into the use of more robust, nonlinear mapping algorithms are leading to discovery of previously hidden relationships. It is expected that future applications of this knowledge will provide strategies for maintaining health and improving medical treatment of chronic disease. REF #4

If nutrition studies could better identify responders and differentiate them from nonresponders on the basis of nutrigenomic or metabolomic profiles, the sensitivity to detect differences between groups could be greatly increased, and the resulting dietary recommendations could be appropriately targeted. Dr. Bland discusses an article by Dr. Steven Zeisel from the School of Public Health and School of Medicine at the University of North Carolina, Chapel Hill, on insights from studies on dietary requirements for choline. REF #5

Moving from a single-nutrient focus to studies on diets, Dr. Bland discusses the research of Dr. Jose Ordovas and his colleagues at the USDA Human Nutrition Research Center on Aging at Tufts University. The discovery of the cardioprotective and other healthy properties of the Mediterranean diet has popularized consumption of Mediterranean products such as olive oil. Molecular, clinical, and epidemiological studies have begun to shed some light about how the various components of this diet may protect the cardiovascular system and decrease the risk of other diseases. It is possible that the right combination of genetic, cultural, and socioeconomic factors is needed to achieve full benefit. REF #6

Nutrigenomics may provide nutritional sciences will a basis to preemptively offset chronic disease. The preemptive model of nutrition consists of multiple independent parts that can be simplified into a number of principle axes. Dr. Bland discusses an article published in *Nutrition Reviews* by Dr. Peter Gillies on a nutrigenomic model for the preemptive nutrition of pro-inflammatory states. He also discusses an article by Dr. Steven Genuis titled "Our Genes are Not Our Destiny: Incorporating Molecular Medicine into Clinical Practice," which was just recently published in the *Journal of Evaluation in Clinical Practice*. And lastly, the subject of genomic and epigenetic approaches to aging is mentioned in terms of the application of high-throughput genomics tools and new opportunities to explore the role and influence of diet. REF #7-9

Genomic Uniqueness: A Clinical Example

Several studies have demonstrated that increases in carotid intima-media thickness (CIMT) is related to cardiovascular morbidity and mortality. In addition, studies have shown relationships between CIMT and cardiovascular risk factors. Dr. Bland refers to a 2001 study published in *Clinical Genetics* in which French researchers examined the relationship between CIMT inter-individual variability and 16 polymorphisms of 11 genes associated with cardiovascular risk factors (genes among lipid and homocysteine metabolism, blood viscosity, platelet aggregation, leukocyte adhesion, and renin-angiotensin system). The interesting finding was that altogether these genes, in men, were able to explain 20.6% of CIMT variability. REF #10

As an additional example—one that points to an area of new research—Dr. Bland cites a 2008 animal study examining the biologic mechanisms by which maternal obesity might exert transgenerational influences on body weight regulation. This study used agouti viable yellow mice. Two separate but contemporaneous populations of mice were studied, one was provided a standard diet and the other a methyl-supplemented diet that induces DNA hypermethylation during development. The researchers tested whether potential transgenerational effects on body weight might be mediated by alterations in epigenetic mechanisms including DNA methylation. The results of this study showed that in a population with a genetic tendency for obesity, effects of maternal obesity accumulate over successive generations to shift the population distribution toward increased adult body weight, and suggest that epigenetic mechanisms are involved in this process. REF #11

Imprinted and More Equal

Dr. Bland lays the groundwork for his interview with Dr. Randy Jirtle with a discussion of some of Dr. Jirtle's publications. In 2007, Dr. Jirtle and his colleague, Dr. Jennifer Weidman, published a very important article in the journal *American Scientist*. As described in this piece, geneticists have always been puzzled by the phenomenon of *imprinting*, in which swaths of DNA on one of a pair of chromosomes are silenced. Dr. Jirtle and Dr. Weidman explain that at a functional level, an imprinted gene is haploid (only one allele works). It is vulnerable to the negative effects of mutations that otherwise would be recessive. Moreover, you can change its function not only with a single genetic mutation, but also with an environmentally induced change to the epigenome—the layer of heritable gene regulation not tied to DNA sequence. As a result of their unique genetic make up, imprinted genes act as nodes of susceptibility. They are—as Dr. Jirtle describes it, using a phrase borrowed from George Orwell's *Animal Farm*—"more equal" in the formation of human diseases. Even more recently, Dr. Jirtle and his colleagues published an article in Genome Research titled "Computational and Experimental Identification of Novel Human Imprinted Genes." REF #12-13

Additional published research that has come out of Dr. Jirtle's laboratory focuses on epidemiological evidence that increasingly suggests that environmental exposures in early development have a role in susceptibility to disease later in life. In addition, some of these environmental effects seem to be passed on through subsequent generations. One study, co-authored by Dr. Dana Dolinoy and Dr. Dale Huang, and published in the *Proceedings of the National Academy of Sciences* in 2007, has gained international attention. This study focused on neonatal exposure to bisphenol A (BPA), and showed that maternal exposure to this endocrine-active compound shifted the coat color distribution of the viable yellow agouti mouse offspring toward yellow by decreasing CpG (cytosine-guanine dinucleotide) methylation in an intracisternal A particle upstream of the *Agouti* gene. Moreover, maternal dietary supplementation, with either methyl donors like folic acid or the phytoestrogen genistein, negated the DNA hypomethylating effect of BPA. REF #14-15

Clinician/Researcher of the Month

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Dr. Randy Jirtle is a professor of radiation oncology and associate professor of pathology at Duke University, where he has been a faculty member since 1977. He holds a bachelor's degree in nuclear engineering and a doctorate in radiation biology from the University of Wisconsin—Madison. Dr. Jirtle's current research focuses on epigenetics, genomic imprinting, and disease susceptibility.

Dr. Jirtle has published over 150 scholarly articles and registered three patents. He serves on the editorial boards of three scientific journals and manages the epigenetics website www.geneimprint.org, which focuses on the quest to understand how environmental factors can affect human disease. Dr. Jirtle was interviewed about his research in a 2006 *NOVA* documentary produced by PBS titled *Ghost in Your Genes*.

Dr. Bland and Dr. Jirtle discuss his epigenetics research and publications at length, including the groundbreaking studies using Agouti mice that have emerged from his laboratory. They touch upon possible future directions for the field of epigenetics.

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